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Colorectal Adenocarcinoma as a Second Malignant Neoplasm Following Wilms' Tumor and Rhabdomyosarcoma

Tamara L. Densmore, MD, Jacob C. Langer, MD, Jean P. Molleston, MD, Louis P. Dehner, MD, and Cheryl M. Coffin, MD

Colorectal carcinoma is one of the most common primary malignancies in adults and occurs in older patients after pelvic radiation. It is rare in children and young adults. We report two cases of colonic adenocarcinoma which were second malignant neoplasms following treatment for early childhood malignancies. One child had Wilms' tumor at 9 months of age treated with preoperative radiation and surgery. He developed radiation colitis and multifocal intestinal adenocarcinomas 42 years later and died with abdominal carcinomatosis. The second child had retroperitoneal embryonal rhabdomyosarcoma at age 1 year and was treated with preoperative radiation, surgery, and chemotherapy. At age 2 years he had radiation colitis; at age 11 years he had rectal adenocarcinoma associated with adenomatous polyps, focal adenomatous change and radiation colitis. Immunohistochemical studies revealed p53 positivity in both adenocarcinomas and in adenomas from the second patient, suggesting that p53 mutation was involved in carcinogenesis. The history of high-dose radiation in early childhood and the multifocal lesions suggest the adenocarcinomas in both patients were second malignant neoplasms, with associated reactive and benign neoplastic and premalignant lesions well documented in one case. These two cases document the phenomenon of early onset of adult type tumors in survivors of childhood cancer and emphasize the need for continued clinical evaluation of patients at risk for second malignant neoplasms.

Key words: second primary malignant neoplasm, colorectal carcinoma, radiation-induced neoplasms, radiation enteritis, p53 mutation

INTRODUCTION

Second malignant neoplasms have been reported with increasing frequency over the past 30 years as a late effect of treatment for childhood malignancy [1–4]. While more effective regimens of radiation and chemotherapy have been responsible for improved survival in pediatric cancer patients, they have also been implicated as a factor in the development of second malignancies. Bone and soft tissue sarcomas and hematolymphoid tumors represent the most common second malignant neoplasms. Carcinomas are relatively unusual in this context, although an association between abdominal irradiation for childhood cancers and adenocarcinoma has been tentatively suggested [5]. Colorectal adenocarcinoma is also rare in children and young adults despite its high frequency in middle-aged and elderly patients. We report two cases of colorectal carcinoma which occurred after Wilms' tumor and pelvic rhabdomyosarcoma were treated with irradiation and multiagent chemotherapy. Immunohistochemical staining of both adenocarcinomas and of associated adenomas in one patient demonstrated the presence of the p53 antigen. These cases document the phenomenon of colonic adenocarcinoma as a second malignant neoplasm in survivors of childhood cancers, associate its development with abdominal irradiation and p53 mutation, suggest a continuum of histopathologic changes in the development of these adenocarcinomas, and emphasize the need for continued clinical monitoring of survivors of early childhood malignancies.

CASE REPORTS

Case 1

A nine-month-old boy was diagnosed with a right renal Wilms' tumor in 1941, which was treated with high-dose irradiation (total dosage unknown) followed by nephrectomy. He was free of disease until 1984 (age 43 years), when he presented with intermittent abdominal cramping, diarrhea, rectal bleeding and weight loss. Diffuse narrowing of the right colon was demonstrated and thought

From the Lauren V. Ackerman Laboratory of Surgical Pathology (T.L.D., L.P.D., C.M.C.), Department of Pathology and Departments of Pediatric Surgery (J.C.L.), and Pediatrics (J.P.M.), Barnes and St. Louis Children's Hospitals, Washington University Medical Center, Washington University School of Medicine, St. Louis, Missouri.

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Address reprint requests to Cheryl M. Coffin, M.D., Department of Pathology, Primary Children's Medical Center, 100 North Medical Drive, Salt Lake City, UT 84113-1100.

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to represent stricture secondary to irradiation. An ileocolectomy with primary anastomosis was performed. A moderately differentiated multifocal mucinous adenocarcinoma involved the ileum and ascending colon. In addition, chronic radiation effect was identified throughout the resection specimen. He developed diffuse peritoneal carcinomatosis and died in 1989 following palliative bypass surgery.

Case 2

A 22-month-old boy presented with an abdominal mass in 1982. Laparotomy revealed a large retroperitoneal tumor which was fixed to the abdominal wall, and a biopsy of the mass revealed embryonal rhabdomyosarcoma. Initial treatment consisted of chemotherapy with cyclophosphamide, vincristine, decarbazine, and doxorubicin and total abdominal irradiation of 2,400 cGY. Residual tumor was resected 7 months later after significant shrinkage. In 1984 a small bowel resection was performed for obstruction due to radiation enteritis. In 1993, at the age of 12 years, he presented with obstipation and weight loss. Physical examination and barium enema revealed a rectal stricture 4.0 cm from the dentate line, and CT scan showed thickening and inflammation in the area of the stricture. He underwent low anterior resection. Pathological examination revealed a moderately differentiated adenocarcinoma, with perirectal fat invasion but no lymphovascular or perineural invasion. The large intestine also contained multiple adenomas, and chronic radiation changes.

MATERIALS AND METHODS

Representative blocks of formalin-fixed, paraffin-embedded tissue were selected from each case for immunohistochemical examination. Deparaffinized tissue sections were stained with antibodies to cytokeratins, carcinoembryonic antigen, carbohydrate 19-9, and antibodies to the p53 antigen using the modified avidin-biotin complex technique [6]. The immunohistochemical reagents are summarized in Table I. Nonimmune rabbit and mouse serum were used for negative controls. Appropriate positive controls were used for each antibody. Reactivity was interpreted as positive or negative.

PATHOLOGICAL AND IMMUNOHISTOCHEMICAL FINDINGS

The ileocolectomy specimen from Case 1 showed diffuse narrowing, ulceration and fibrosis of the cecum and mucosal irregularities in the ascending colon. The well-to-moderately differentiated adenocarcinoma extended onto the serosa. Some areas of the tumor were mucinous with tumor cells floating in pools of mucin and areas of signet ring differentiation. Focal neuroendocrine differentiation was present. Perineural and lymphovascular invasions were identified. Chronic radiation changes in the intestine included medial and intimal vascular thickening, mural fibrosis, focal fat necrosis and a scattered mononuclear inflammatory infiltrate.

TABLE I. Immunohistochemical Reagents

Antibody[a]	Source	Dilution
Cytokeratin cocktail (CKC)		
AE1/AE3	Boehringer-Mannheim, Indianapolis, IN	1:150
MAK-6	Triton Biosciences, Alameda, CA	1:40
CAM 5.2	Becton-Dickinson, Mountain View, CA	1:150
Cytokeratin 20 (CK20)	Dako, Santa Barbara, CA	1:40
Carbohydrate 19-9 (CA 19-9)	Signet, Dedham, MA	1:100
Carcinoembryonic antigen	Boehringer-Mannheim, Indianapolis, IN	1:400
p53 epitopes		
DO1	Oncogene Science, Uniondale, NY	1:80
DO7	Dako, Santa Barbara, CA	1:80
1801	Oncogene Science, Uniondale, NY	1:80

[a]All monoclonal antibodies.

The rectosigmoid colectomy from Case 2 contained a 3-cm partially ulcerated tumor which constricted the bowel lumen. Four separate polyps were also identified. The nonmucinous moderately differentiated adenocarcinoma extended into surrounding perirectal fat (Fig. 1). No lymphatic or vascular invasion was identified. Three polyps were tubular adenomas, one was a juvenile polyp, and there were multiple foci of adenomatous changes. The rectosigmoid colectomy showed chronic radiation changes (Fig. 2).

Results of the immunohistochemical stains are summarized in Table II. Staining for cytokeratins, CEA, and CA 19-9 was nonspecific and uniformly positive in all lesions studied, including the inflammatory polyp. The adenocarcinomas from both patients stained for the 1801 and DO7 epitopes of p53 (Fig. 3). p53 immunoreactivity was also detected in focal adenomatous change and tubular adenomas but with a less strong, less diffuse pattern of reactivity. No p53 staining was identified within the inflammatory polyp or nonneoplastic mucosa.

DISCUSSION

Although the annual incidence of colonic adenocarcinoma in individuals under 20 years of age is approximately 1 in 10,000,000, it is the second most common digestive tract malignancy in the pediatric age group after liver tumors [7,8]. The majority of cases are in the second decade of life, but cases have been reported in infancy and in the first decade of life. Most reports confirm a

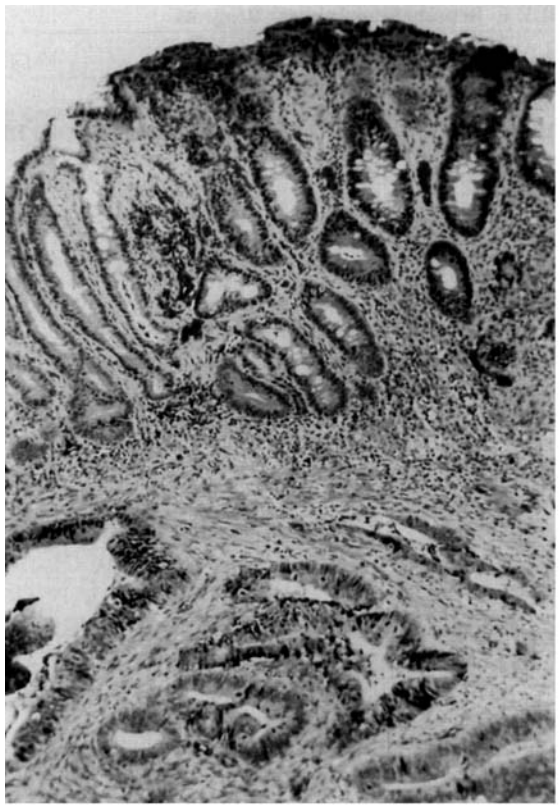

Fig. 1. The moderately differentiated adenocarcinoma in Case 1 forms irregular glands with an infiltrative pattern and a desmoplastic stroma (hematoxylin-eosin, × 100).

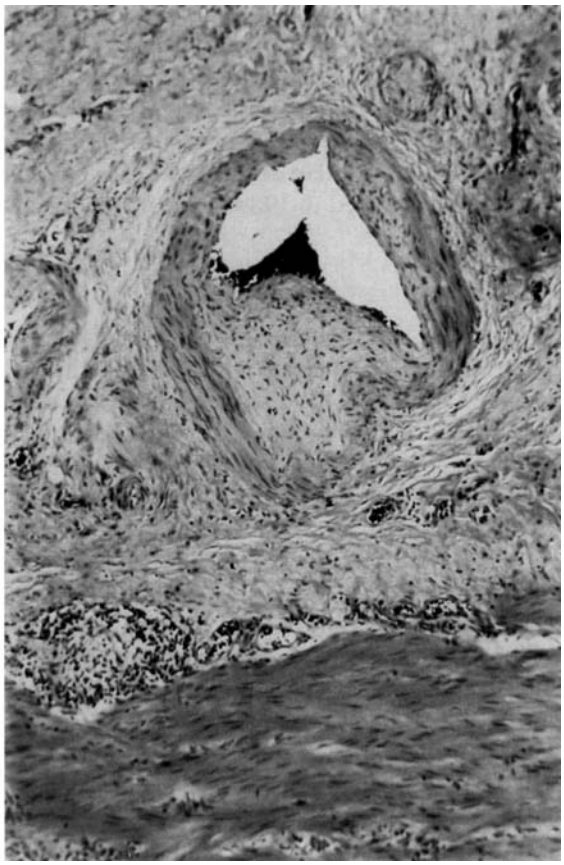

Fig. 2. Chronic radiation colitis displays fibrosis and medial and intimal thickening of blood vessels (hematoxylin-eosin, × 200).

predilection for males with nonspecific and vague symptoms of abdominal pain, distension, anemia, emaciation or mass. Risk factors for colorectal carcinoma in children and adolescents overlap to some extent with those for adult patients, especially with regard to genetic conditions and precursor lesions. Approximately 10% of cases have known precancerous conditions including various forms of polyposis and inflammatory bowel disease [9,10]. Cases of colorectal carcinoma have been reported as a second malignant neoplasm following abdominal irradiation for other malignancies in early childhood, mainly Wilms' tumor [5,11,12].

A link between radiation and colorectal carcinoma was initially postulated based on the observation of an increased frequency of colorectal adenocarcinoma in atomic bomb survivors in Hiroshima and concentration camp victims of irradiation experiments [13,14]. Studies in survivors of gynecologic malignancies further strengthened this association by showing development of colorectal carcinoma within the field of radiation [15–17]. Since the initial reports, it has become clear that colorectal carcinoma may follow lower doses of radiation or single doses of massive radiation [15,16]. The interval between radiation and development of colorectal carcinoma can be very long, with greater than 60% of cases occurring between 11 and 30 years following radiation exposure [14,18]. Colorectal carcinoma as a second malignant neoplasm is distinctly unusual in the pediatric age group [5,11,12,19–21]. The two cases we report further document the phenomenon of colorectal adenocarcinoma as a second malignant neoplasm in this context. The link

TABLE II. Immunohistochemical Staining

	Case 1	Case 2			
Marker	CA	IP[a]	FAC[b]	AP[c]	CA[d]
CKC	+	+	+	+	+
CK20	+	+	+	+	+
CEA	+	+	+	+	+
CA 19-9	+	+	+	+	+
1801	+	−	−	+	+
D01	−	−	−	+	+
D07	+	−	+	+	+

[a]IP, inflammatory polyp.
[b]FAC, focal adenomatous change.
[c]AP, tubular adenomas.
[d]CA, adenocarcinoma of the colon.

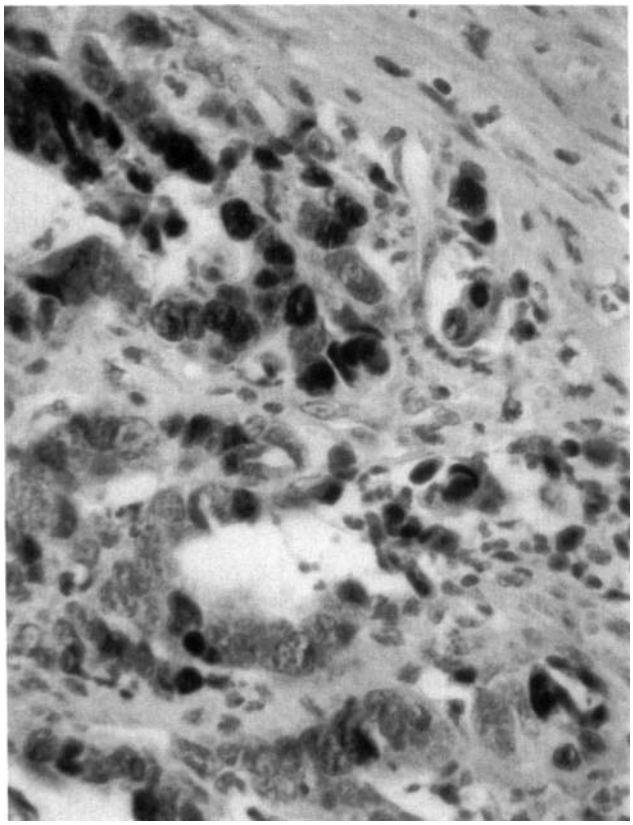

Fig. 3. p53 staining is demonstrated of nuclei of the adenocarcinoma from Case 2 (p53 immunostain, × 400).

between radiation and colorectal carcinoma is supported in these two patients, both of whom received high-dose radiation therapy prior to resection of their original tumors. The interval between treatment and development of the second malignant neoplasm was greater than 10 years in both and was accompanied by vague abdominal symptoms, weight loss and strictures. Both arose in a background of radiation colitis. The nonspecificity of the gastrointestinal symptoms may have delayed definite diagnosis of carcinoma in both patients.

One child (Case 2) had the additional pathologic findings of focal adenomatous change and tubular adenomas in the colon. Whether these lesions were related to radiation therapy or to another cause, such as an underlying genetic predisposition to colorectal carcinoma, is uncertain. However, there was no history of a familial cancer syndrome including the Li-Fraumeni syndrome in either patient. The finding of mutant p53 antigen in the preneoplastic adenomatous lesions from one patient and in both adenocarcinomas indicates that mutation of the p53 tumor suppressor gene was involved in the adenoma-carcinoma sequence. Although described as a rare finding in preneoplastic adenomatous lesions, it has been shown that positive immunohistochemical staining for p53 correlates with point mutations of the p53 gene [22,23]. Some investigators have suggested that the rarity of this mutation in adenomas indicates that it is a late occurrence in the development of carcinomas [24,25]. It is also possible that the rhabdomyosarcoma in Case 2 was an initial manifestation of the Li-Fraumeni cancer family syndrome, which is associated with a germline p53 mutation but not intestinal carcinoma, of adenomatous polyps coli, or of a nonpolyposis colonic cancer family syndrome. Neither case could be evaluated for presence of APC gene mutations at the time of diagnosis or retrospectively. It is more tempting to speculate that radiation therapy induced a p53 mutation in these two cases and resulted in malignant transformation.

Whatever the pathogenetic mechanism, as the survival for childhood cancer improves, second malignancies will become increasingly common. These two cases document the phenomenon of early onset of adult type tumors in this clinical setting and illustrate the nonspecificity of early gastrointestinal symptoms in young patients with intestinal adenocarcinomas. These phenomena emphasize the need for continued clinical evaluation of patients who have been treated with radiotherapy for childhood solid tumors. Patient education about signs and symptoms of second malignancies, careful attention to the medical history and chief complains, and early diagnostic evaluations when problems develop are warranted based on these cases.

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